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I. OBJECTIVE

The main objective of this research project is the development of a non-invasive method and instrument for head injury detection and monitoring using a new approach based on ultrasonic and low-frequency acoustic (ULFA) soundwave detection.

II. TECHNICAL INVESTIGATION

Over the past year, we have accomplished the following tasks: (1) developed an integrated portable ultrasonic acquisition device for clinical use; (2) performed human studies where we acquired transcranial ultrasonic signals from head-injured patients and normal volunteers; and (3) developed software tools to evaluate the information content of transcranial ultrasound signals.

II.a Background: Self-Referenced Detection

This study represents the initial human studies in our investigation of a unique technique for in vivo measurement based on "self-referenced approach". Self-referenced (or differential) techniques are a promising class of detection methods for *in vivo* diagnostics. It can be very difficult to measure the absolute value of some physical property of tissue inside the body due to variations in the overlying tissues among the population. What is required is some standard that lies on a similar path as the tissue of interest. An example is the measurement of absolute backscatter of certain regions of heart tissue. The blood in the chambers of the heart can be used as a reference scatterer of ultrasound to normalize the backscatter data from parts of the ventricular walls. The difficulty with this specific method is the large dynamic range required since blood scattering is relatively weak and often below the background noise level of a system built to capture backscatter from tissues. However, the brain presents a unique opportunity for the application of self-referencing methods since it is the only organ in the body whose structure and location has a left-right symmetry relative to the median plane. Thus the median plane can be thought of as a mirror and to some approximation, the two hemispheres of the brain are (structurally) mirror images of each other. Thus one might expect the ultrasonic properties along the path of a propagating wave through the tissue should be similar in the region symmetrically placed in the other hemisphere, at least for

normal healthy tissues. For example, one may non-invasively acquire ultrasound data from a white matter region in the right hemisphere through the right temporal region of the skull. Then one can make the same measurement for the left side. One would expect there to be some similarity in the two signals for a normal brain. Although each signal must traverse a different piece of the skull these overlying structures will have similar impacts on the ultrasonic signals passing through them because of their symmetric positions.

The ultimate goal is to acquire transcranial ultrasonic signals from opposite sides of a subject's head to identify differences and to correlate those differences with space filling pathologies. Because of the attenuating effects of the skull and because these effects become stronger with increasing frequency we use lower frequency ultrasound than is used in imaging applications. Our task is not to form images but to detect conditions consistent with space-filling pathology and thus reliable transmission across the skull is more important than tight spatial resolution. The task before us is to evaluate the signals captured using this lower frequency ultrasound, and specifically to understand the types of signal features we are able to reliably acquire.

II.b Human Studies – Initial Trials with Head Injured Patients and Normal Volunteers

In collaboration with the Neurosurgery Department of the University of California at San Francisco Medical School (Dr. Martin Holland), in late January 2001 we acquired data from three head injured patients admitted to the intensive care unit of San Francisco General Hospital. Data were also acquired from two normal volunteers. These human studies were performed in accordance with the protocols and procedures approved by the Internal Review Boards (IRBs) of the University of California San Francisco and Oak Ridge National Laboratory/Oak Ridge Institute for Science and Education. The initial protocol called for regular acquisitions of CT scans (a standard imaging procedure for head-injured patients) along with our backscatter ultrasonic data. We thus proceeded with a study using the patient population (three patient) that was available to us at the time. Of the three patients, one was comatose from an injury sustained due to a fall some weeks before being enrolled in the study. This patient had the portions of his parietal and

temporal skull bone removed on the left side of the head. The right side of the skull was intact. Subject two was a newly admitted stroke patient who was conscious and reactive to verbal requests. Patient three had an aneurysm in the frontal lobe and was admitted unconscious and remained in that state throughout the study. This patient under went brain surgery and data were acquired from the subject both pre- and post-operatively. In total, we have collected over 1,100 waveforms in this clinical study.

II.b.1 Instrumentation and Methods

For this study we assembled an integrated, portable ultrasound acquisition system. Photos and a schematic of this system are shown in Figure 1. The main enclosure houses both the pulser/receiver unit and the digital oscilloscope and thus provides for the generation of ultrasound and the digitization of acquired signals. A small compartment in the top of the enclosure houses a laptop computer. The laptop interfaces to the system via GPIB (General Purpose Interface Bus) and controls the signal acquisition process. The control software is a custom-written LabView program that permits detailed management of the acquisition process and data storage. For the human studies, the system was used in a single transducer mode where the probe both generates the ultrasonic pulse and receives the backscattered signals. Most of the data were acquired with a 1-MHz center frequency transducer while a 500-kHz probe was used for all other cases.

During acquisition of patient data, one operator placed and held the transducer on the patient, while a second operator managed the control software. Although the system can be modified to permit single-user operation, the two-person team was designed to make the most efficient use of the study time. The operator holding the transducer manipulated the probe on the subject's temporal region and monitored the signal on the oscilloscope screen on the instrument panel. Once a signal was judged to represent valid data, the second operator would trigger the data capture process from the laptop. Over the course of the next several seconds, 10 waveforms were captured and saved to the laptop hard drive. Each captured waveform actually represents the average of many raw waveforms. The oscilloscope captured and averaged the raw signals and then the laptop downloaded the averaged waveform from the oscilloscope memory. The digitized waveforms consist of 10,000 points, with sampling rates of 10 pts/µs (i.e., 10 digitized

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points per 10^{-6} seconds) and 2.5 pts/µs. The sapling rate of 10 pts/µs permitted acquisitions up to depths of approximately 3", while the 2.5 pts/µs sampling rate permitted acquisition of signals over the entire width of the head. The transducers were coupled to the head using Aquasonic Ultrasound Transmission Gel (Parker Laboratories, New Jersey, USA). The positions of the transducers during the study were recorded relative to the top-front of the ear/head union (see Figure 2). The distance from this landmark and rotation angle was registered in each case. The angle was measured relative to the line joining the ear/head notch and the near corner of the eye.

II.b.2 Results

General Features of Waveforms

Figure 3 shows representative waveforms captured from patient one for depths less than 3". This patient had the left side of his skull removed. Thus on the left side, ultrasound could be launched non-invasively through the scalp and directly into the brain. On the right side, the ultrasound had to pass through both scalp and skull before entering the brain. These data illustrate the effect of the skull on the ultrasound propagation. In Figure 3a, the waveform taken from the left side (skull removed) is shown. The backscattered signals near the transducer are large, followed by some low signal areas and some large features at about 50 µs (1.5 in. deep into the head). The near echoes (< 8.5 µs or 1/4" in depth) are ringdown artifacts from the transducer excitations and interface artifacts of the transducer/coupling gel/scalp system. This region is followed by backscatter from within the scalp and terminates at the reflection just short of 17 µs (1/2") due to the scalp/meningeal/brain interface. The ultrasonic impedance of the scalp is reasonably well matched to that of the brain and the higher-order echoes are small. Thus the small signals from 20 to 45 µs (depths of approx. 0.75" to 1.25") are probably due to scattering events inside the brain. The large features from 45 to 55 µs (1.25" to 1.6") appear to be echoes from within brain, likely caused by an interfacial reflection. These could be due to the lateral ventricle or the cortex fold between the upper and lower parts of the brain. This feature consists of three overlapping wave packets. In Figure 3b, the backscattered waveform from the right side of the head (skull intact) is shown. Here

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most of the signal is confined to a region < 45 µs (1.25"). These signals are consistent with a model of multiple reverberations in a three-layer medium (e. g., the scalp/skull/brain) with all the signals originating in the first two layers. These reverberations in the overlying structures likely mask any signals from echoes or scattering within the brain.

Figure 4 shows representative waveforms captured from patient one for depths that cover the entire width of the head. Figure 4a shows the waveform taken from the left side (no skull bone) of the head. One can see the weak isolated echo originating from a depth of about 6.75". Figure 4b shows the waveform taken from the right side of the head. Here, we observe a large echo train starting at a depth of about 6.75". This type of echo train is indicative of reverberations in a single layer of finite width. Here the primary echo is from the brain/scalp interface. The second echo is due to the reflection off of the scalp/air interface, while the third is from a reverberation in the scalp layer. Because of the large mechanical mismatch between brain tissue and bone, one might expect that the echo in the former waveform (Fig 4a) should be larger. However, this is clearly not the case. This can be explained by roughness and/or non-normal orientation of the inner surface of the skull. The echo portion of these signals in shown in more detail in Figure 5.

Development of Analysis Tools

In this study we have acquired large volumes of data and mining the data for relevant information is a formidable task. Many of the analyses and comparisons we need to perform are unique and thus require custom-written software tools to be effectively executed. Using LabView, a rapid application development (RAD) environment, we are able to create the required tools in an efficient manner. LabView is a cross-platform application that provides a wide variety of user interface widgets as well as sophisticated signal processing tools as predefined objects. This permits the programmer to concentrate on developing the high-level analysis algorithms and frees one from having to build the low-level interface and analysis elements. In Figures 6, 7, and 8 we show three examples of data analysis and management tools we have developed specifically for the human studies data using LabView.

III. CONCLUSION

During this reporting period, we have achieved several very important milestones. We have demonstrated the acquisition of ultrasound signals from normal volunteers in the lab and head-injured patients in a hospital setting. We have analyzed and compared waveforms to evaluate lesion detection strategies. We have also begun to identify the types of signal features in the intracranial backscatter that can provide useful information. Using the knowledge we are gaining from this study, we are refining our detection strategies and planning for more specific and targeted data acquisitions for the second round of human studies. The data analysis process is on going as we have over 1,100 waveforms collected in this study and a wealth of information to be distilled from them. As stated in previous reports our approach to ultrasonic brain monitoring is focused on signal processing; this is in contrast to traditional approaches to the diagnostic applications of ultrasound that are more probe-centered (e.g., using multiple sophisticated probes or phased-array systems). We believe that our results show that the signal processing approach is feasible and we think that with more data we can establish clinically relevant correlations between features in the non-invasively captured backscattered signals and pathological conditions inside the cranium.
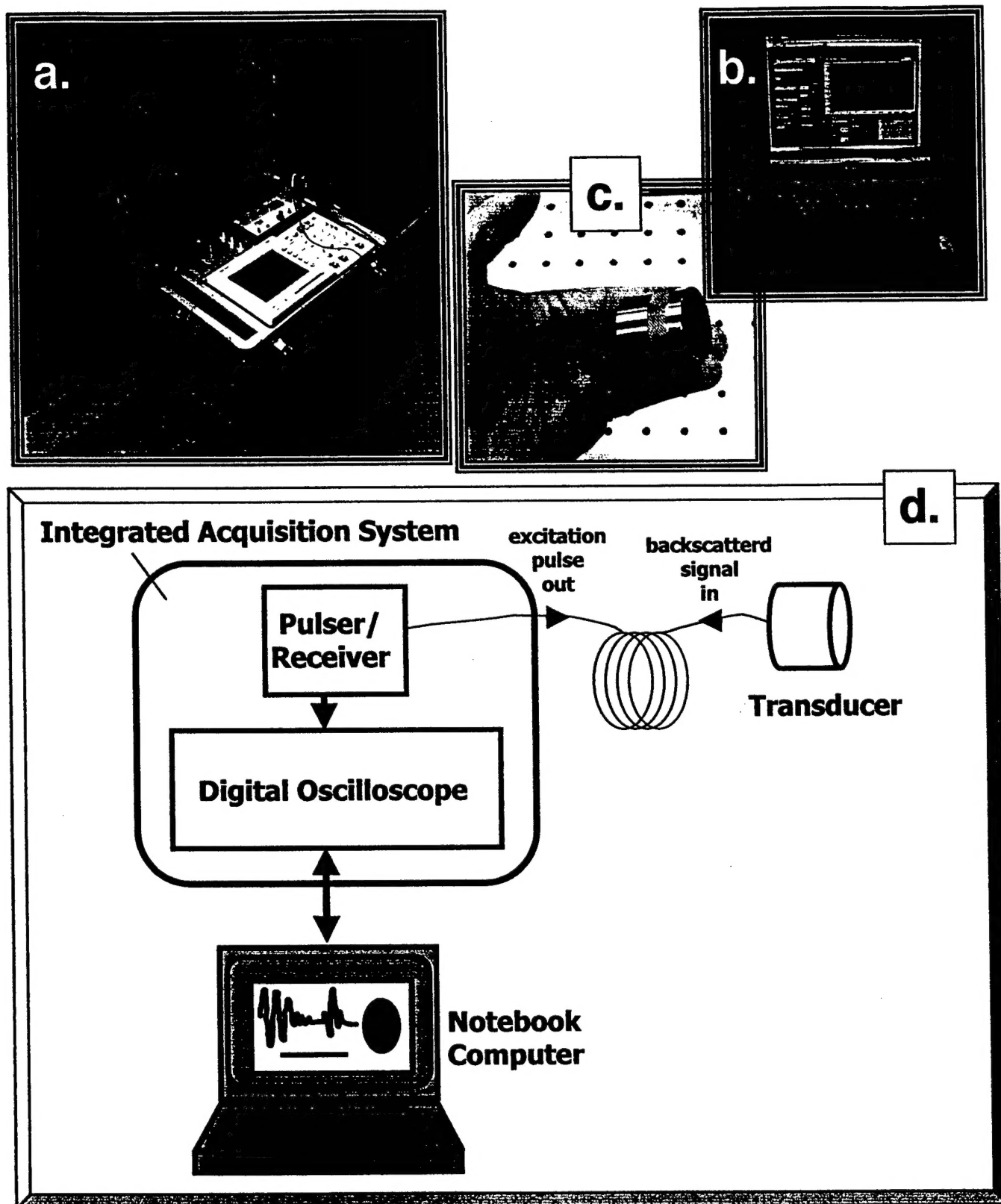
Figure 1 - The ultrasound acquisition system. (a) The integrated instrument houses the pulser/receiver unit and a digital oscilloscope for generating pulses and capturing detected waveforms. **(b)** The laptop computer running the control software for the acquisition system. **(c)** One of the transducers used in this study. **(d)** Schematic diagram of the acquisition system.

position of transducer

corner of eye

"notch" of ear
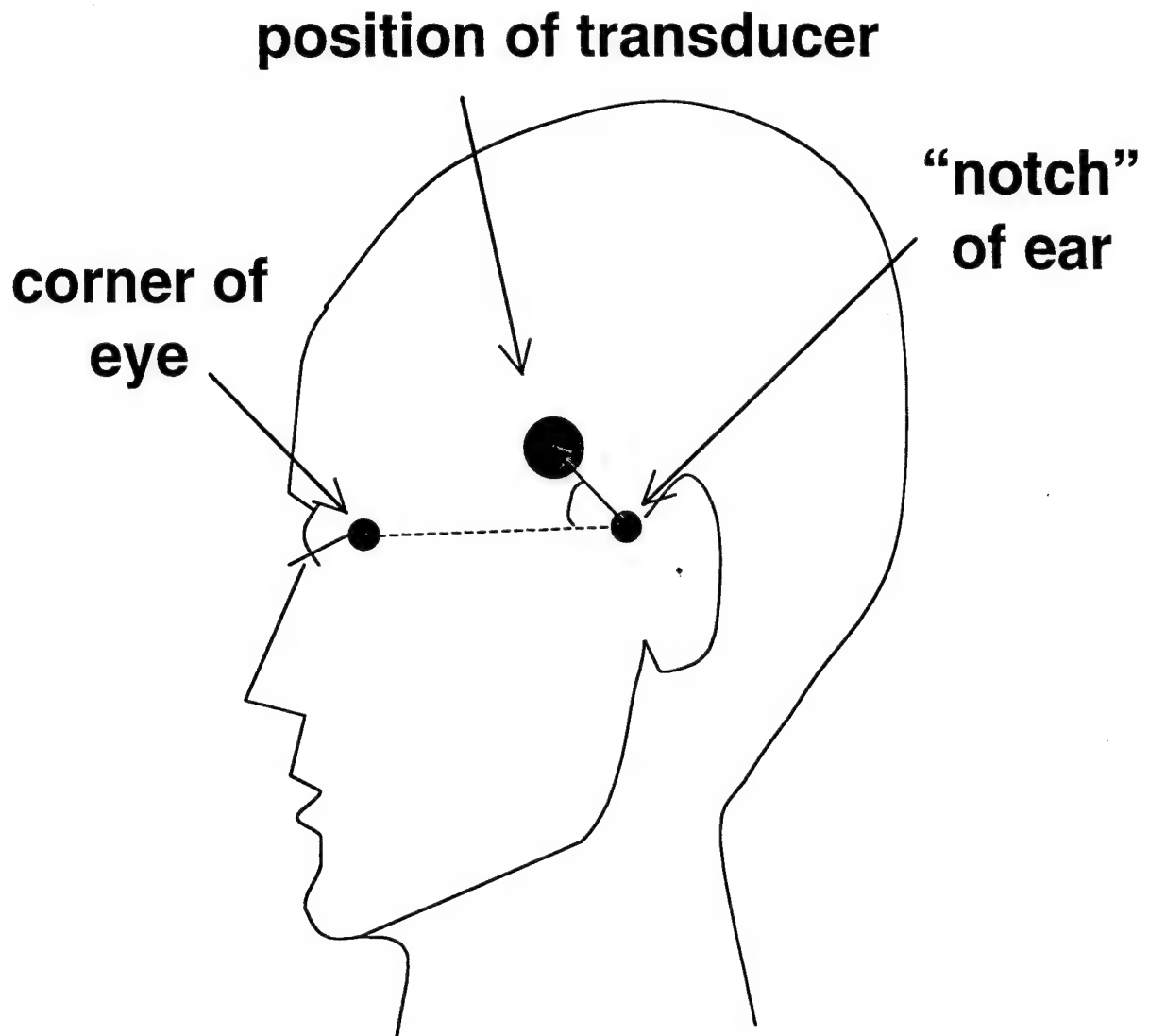
Figure 2 - System for recording transducer position. The position of the transducer for a given acquisition was recorded as the distance from the "notch" where the ear joins the head and the rotation angle relative to the "notch" and the corner of the subject's eye.
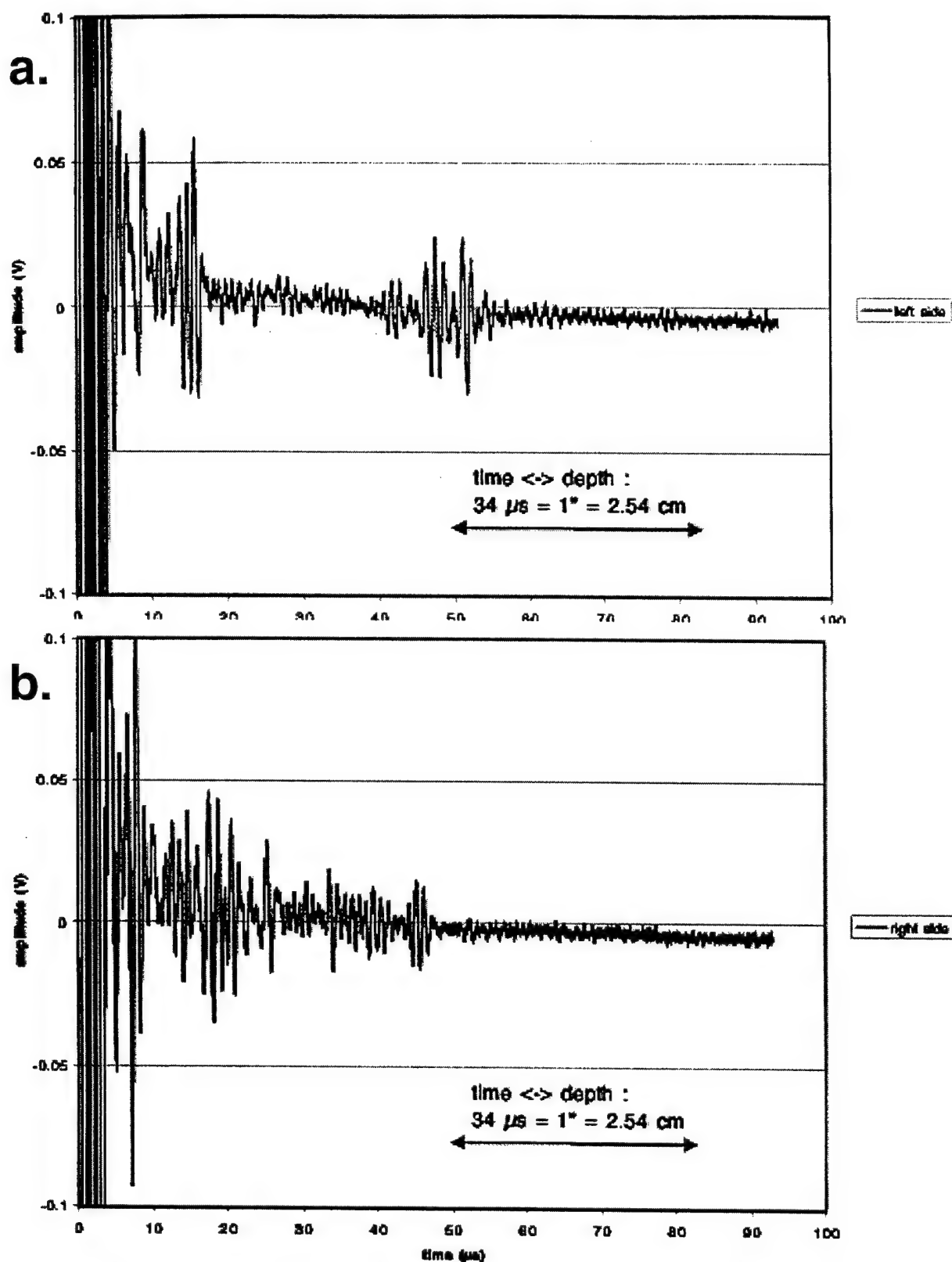
Figure 3 - Waveforms captured from Patient 1 from depths < 3 ". (a) Waveform captured from the left side of Patient 1. The skull bone had been removed on this side. (b) Waveform captured from the right side of Patient 1. The skull bone was intact on this side. The depth is one-half of the total travel distance (out and back) of a given signal segment. Both signals were taken from similar positions near the temple.
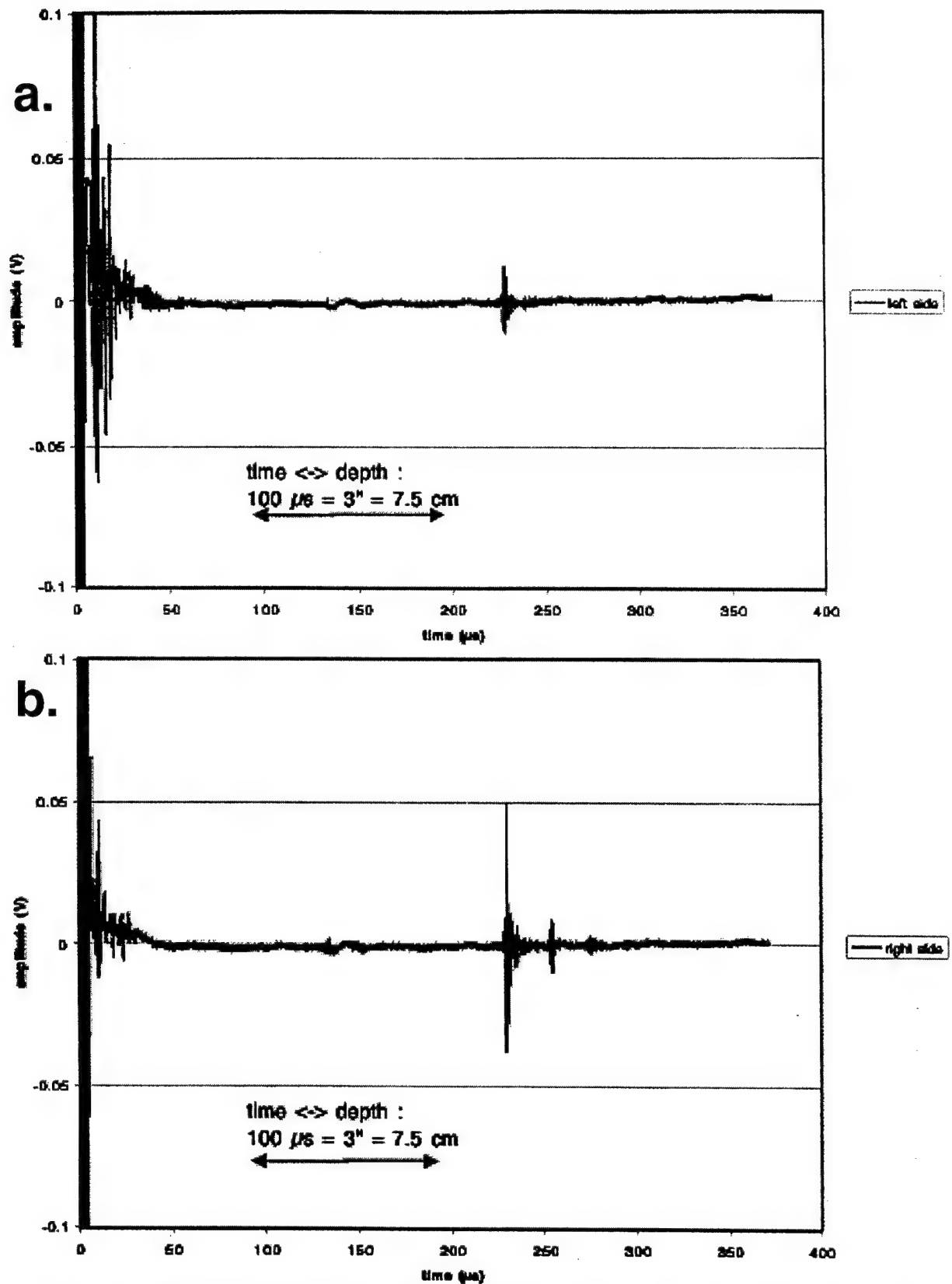
Figure 4 - Waveforms captured from Patient 1 from across the entire cranium.
(a) Waveform captured from the right side of Patient 1. The skull bone was not present on this side. The single echo beyond 200 μs is the reflection off of the skull. (b) Waveform captured from the right side of Patient 1. The skull bone was intact on this side. The series of echoes beyond 200 μs are from reflections off of and reverberations in the scalp.

right side
left side

time <-> depth :
100 μs = 3° = 7.5 cm

200   250   300   350

time (μs)
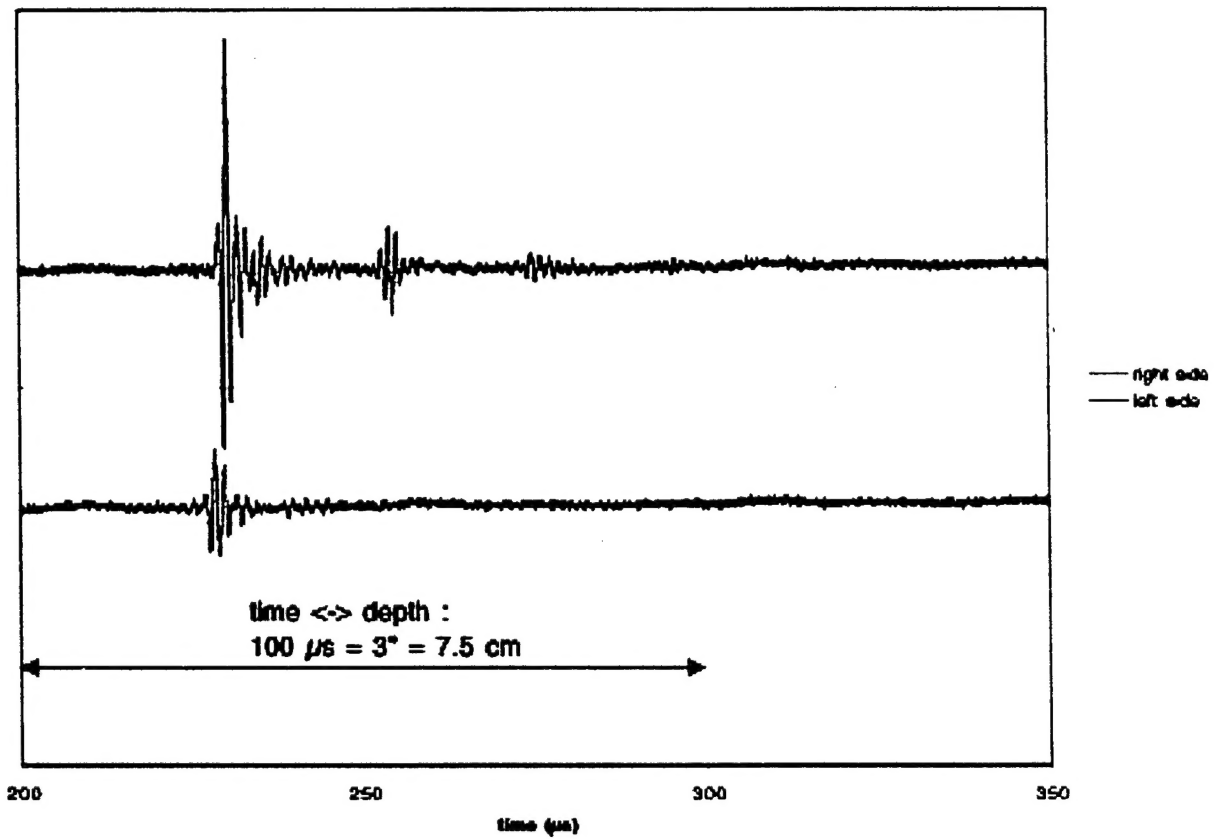
Figure 5 - Zoom in on the echo regions of the waveforms shown in Figure 4.
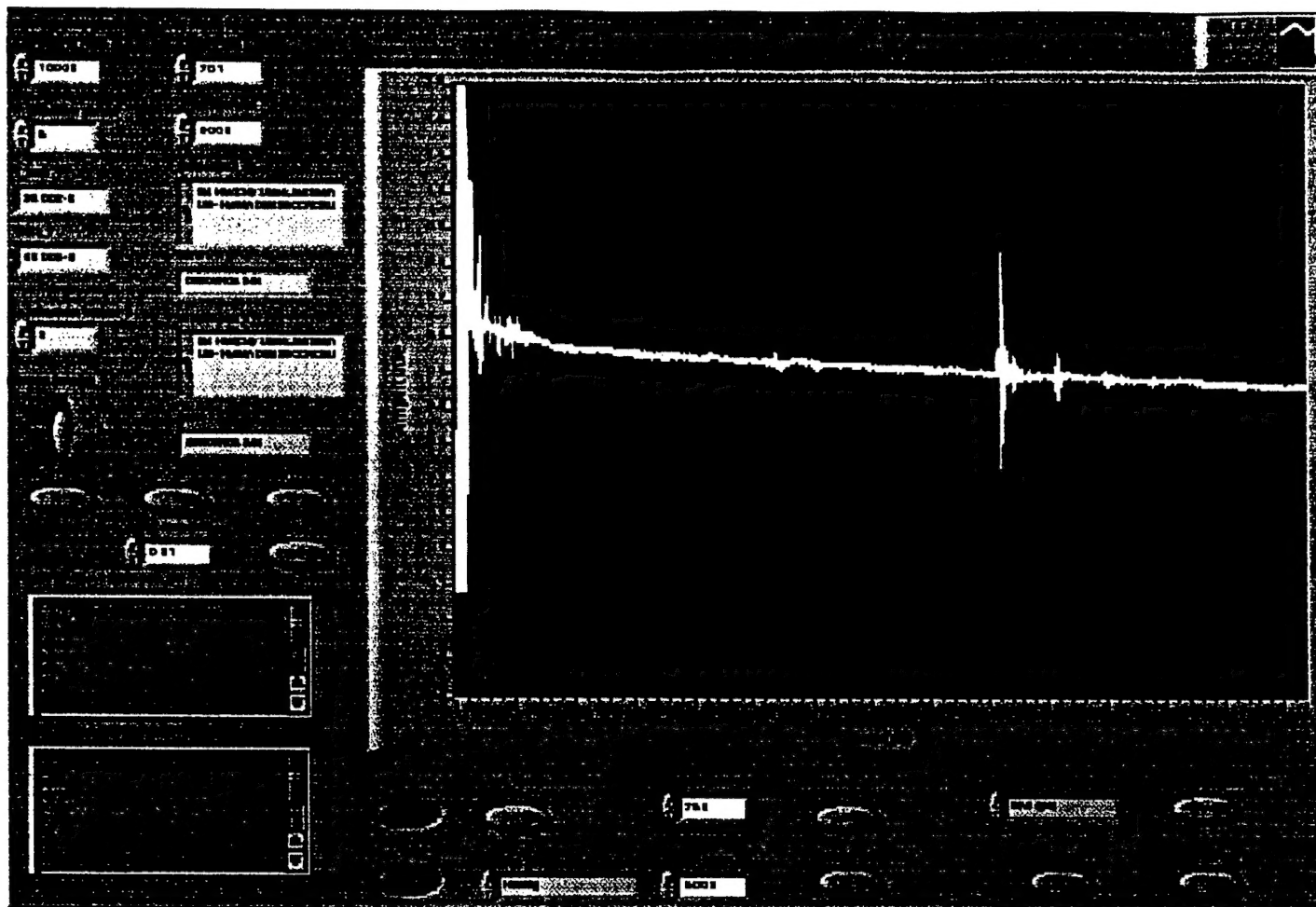
Figure 6 - Waveform Comparison Software. The front panel of a custom written LabView application for comparing waveforms acquired in this study. This program permits the comparison of feature sizes and positions across or within datasets. The waveforms shown above were taken from the left and right sides of Patient 1 and include signals from the entire width of the subjects head.
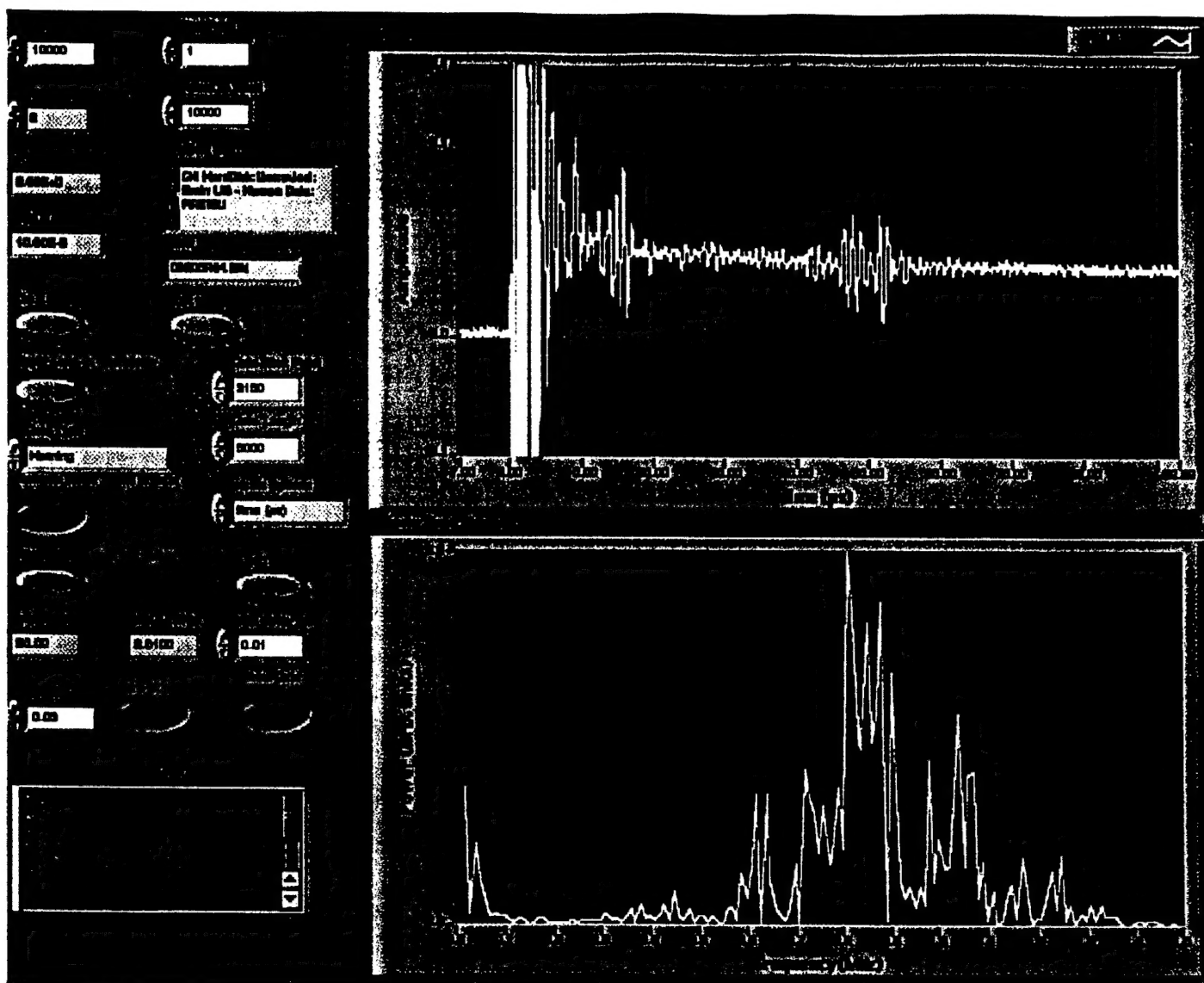
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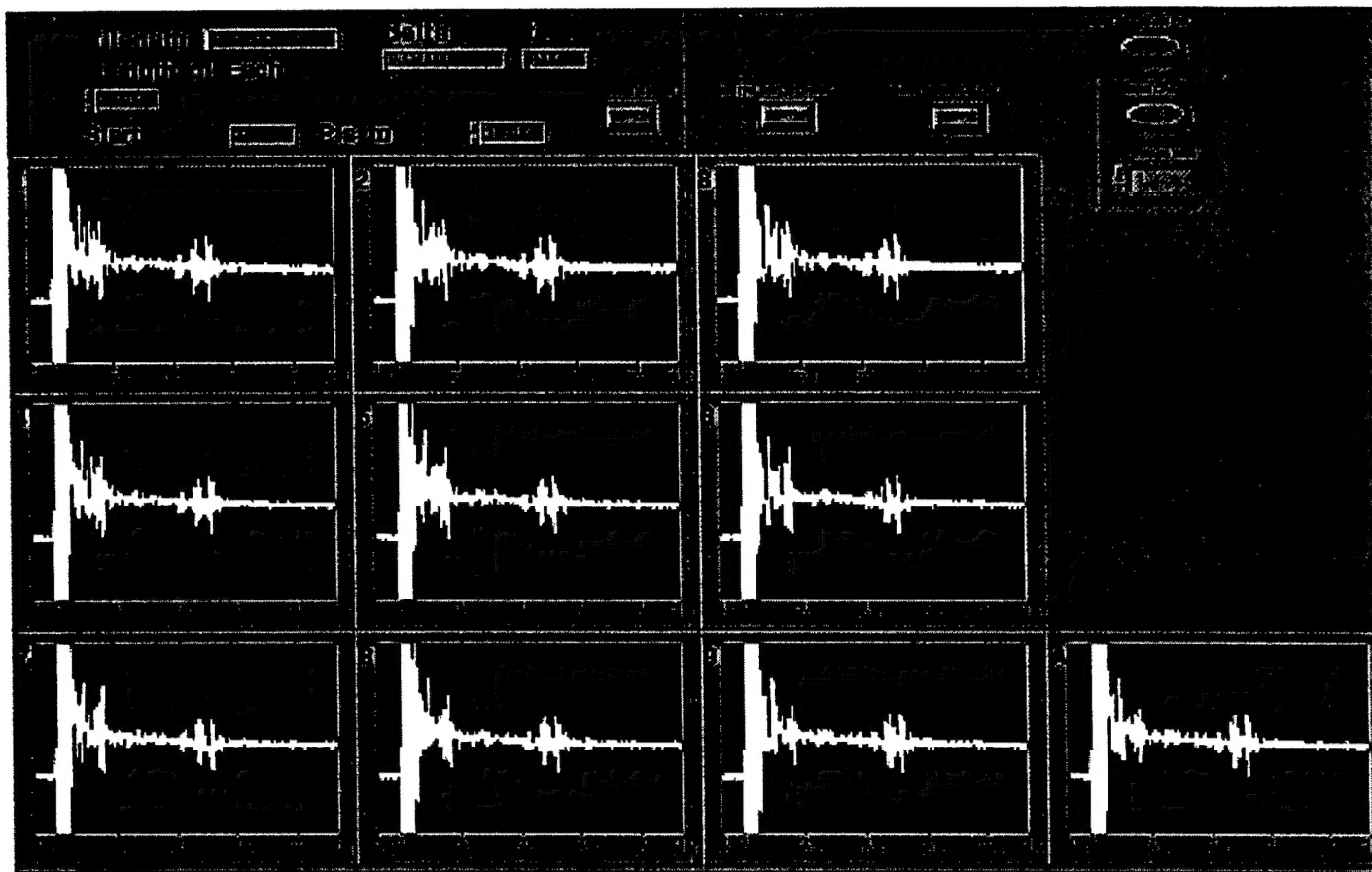
Figure 8 - Custom Data Browser. The front panel of a custom written LabView application for browsing the all the waveforms from a particular data set. This program is also used to extract waveforms to ASCII files for importing into commercial analysis and plotting applications